

The role of ragweed pollen in autumnal asthma*

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Thirty-nine ragweed-allergic seasonal asthmatics were studied from 1972 to 1974. After quantitative skin tests, antigen E-induced leukocyte histamine release, quantitative inhalation bronchial challenge with ragweed extract to determine PD_{35} (provocation dose of allergen causing 35% decrease in specific airways conductance), and radioallergosorbent test (RAST) determinations were done, patients were paired based on PD_{35} values and randomly assigned to treatment or placebo groups, receiving either aqueous ragweed extract or placebo prior to the 1973 ragweed season. Treated patients received a mean cumulative dose of extract equivalent to 11.7 μ g antigen E (4,180 protein nitrogen units [PNU]). Twenty-nine patients were followed through the ragweed season with daily symptom diaries and biweekly physician examinations. Severity of disease was not predictable by PD_{35} data, skin tests, leukocyte histamine release, or radioallergosorbent test (RAST) values. Although all patients were ragweed-allergic by objective tests, only 13/29 had asthma symptoms correlating with ragweed counts. Mold spore counts were related significantly to symptoms in some patients. Asthma and hay fever symptoms correlated significantly in 24/29 patients. This dose of immunotherapy caused no significant difference to be found in asthma or hay fever symptoms in treated versus placebo patients for the 1973 reporting period as determined by physician evaluations or daily symptom diaries. No patients showed significant improvement in PD_{35} values after treatment in 1973. Similar findings were obtained for a smaller group of patients followed through the 1974 ragweed season who received a mean dose of 31.2 μ g antigen E (11,140 PNU). The failure of these patients to show a response to immunotherapy could be due to a combination of the relatively low dose of ragweed extract and their sensitivity to other allergens.

There is a long-standing clinical observation that, at the height of the pollen season, some patients with hay fever have asthma as well. In addition, it is stated¹⁻³ that immunotherapy may be expected to relieve asthma more readily than hay fever symptoms. A controlled study of treatment of asthma associated with ragweed allergy indicated that 15/22 children with pollen asthma lost their asthma while receiving desensitization injections of pollen extract, whereas only 1/14 controls showed loss of asthma.⁴ This difference was highly significant. This study was performed before the techniques for immunologic study we have used in our hay fever studies were de-

veloped. Citron, Frankland, and Sinclair⁵ reported in 1958 that 12 of 13 grass-sensitive asthmatic patients had a significant decrease in bronchial sensitivity to inhalation of grass pollen extracts after 3 months of preseasonal hyposensitization with grass pollen extract. Improved bronchial tolerance correlated with improved asthma symptoms during the subsequent pollen season. Five control patients showed no significant change in bronchial tolerance on repeat challenge. McAllen⁶ reported improved bronchial tolerance to grass pollen extract inhalations in only 4 of 40 patients being treated with injections or inhalations of grass pollen extract. However, in children treated for 2½ to 3 years with house dust extracts, 45 of 52 patients had "marked" improvement of bronchial tolerance.⁷

In our previous studies of ragweed hay fever patients, we have found good correlation between quantitative skin testing, leukocyte histamine release to antigen E, RAST, and seasonal average symptom scores in untreated patients.⁸ Furthermore, the daily pollen count commonly correlated well with the

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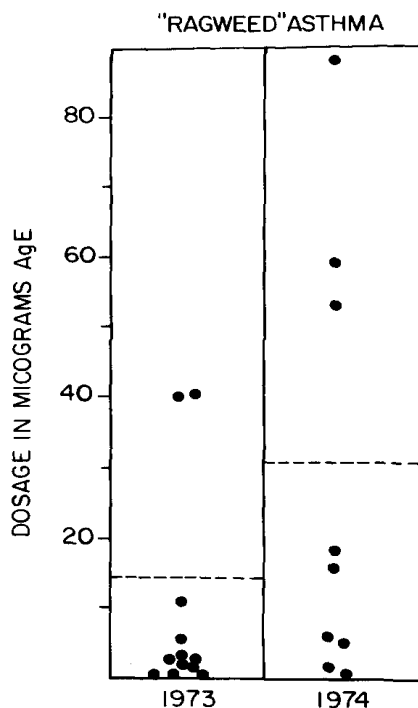


FIG. 1. Dosage of antigen E received ($\mu\text{g/ml}$) in treated patients for 1973 and 1974.

symptom scores reported on that day.⁸ We proposed to study similar factors in ragweed-allergic asthmatic patients. Since we have been involved for some time in the study of treatment for ragweed hay fever, we also proposed to study the effects of immunotherapy in ragweed-allergic patients with seasonal asthma during the late summer and early fall, correlating our clinical observations with various immunologic measurements.

Although the doses of ragweed pollen extract we were able to administer were lower than those we have used in recent studies of hay fever, they were as large as those which produced a significant improvement in earlier studies of hay fever.⁹ Consequently, these studies represent only a test of low to modest dose immunotherapy in asthma. Nevertheless, this report is presented now because examination of the correlations between pollen and mold sampling and symptoms and between immunologic tests (including bronchial challenge) and symptoms throw doubt on some of the assumptions commonly made as to the role of ragweed pollen in seasonal asthma.

MATERIAL AND METHODS

Screening questionnaires were sent to 300 patients responding to newspaper announcements about studies of immunotherapy and asthma. Of those returning the questionnaires, 79 indicated a history of asthma in the ragweed season and were evaluated by a physician in the clinic

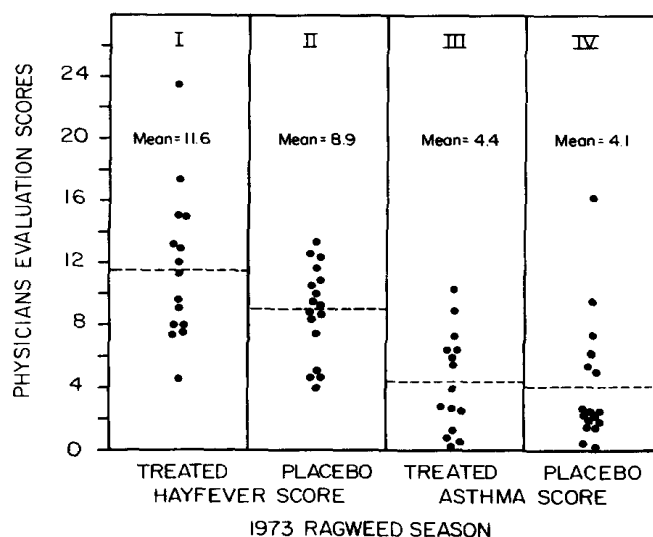


FIG. 2. Individual and mean hay fever and asthma scores from physician evaluations for treated and placebo patients during 1973 ragweed season.

between September, 1972, and March, 1973. After a history and physical examination were performed, patients were tested on the volar aspect of the forearms to crude ragweed pollen extract (Center lyophilized lot No. 16608 FD), ragweed antigens E,* Ra3,* Ra5,* and extracts of mixed grass pollen, mixed tree pollen, mixed mold spores, and house dust (Greer Laboratories, Lenoir, N. C.). Antigens were diluted in Tris buffer containing 0.03% serum albumin as a stabilizer. The skin testing technique has been described more fully elsewhere.⁸ Solution, 0.05 cc, was injected intradermally and the reaction read at 15 minutes. Patients having positive skin tests to crude ragweed at 1×10^{-2} μg of protein nitrogen per milliliter (1 PNU) were tested with serial dilutions until the concentration required for a threshold 2+ reaction was determined. A 2+ reaction was defined as 10 mm of wheal and 20 mm to 30 mm of erythema measured in two dimensions.

Thirty-nine patients were selected on the basis of symptoms of asthma in the ragweed season, but no perennial asthma, no immunotherapy in the previous two years, and a positive skin test to ragweed, for further studies described below. Twenty-nine patients completed all the 1973 studies. Four additional patients completed part of the studies.

The patients returned to the clinic on a separate day for baseline leukocyte histamine release and quantitative bronchial challenge. The patients were instructed not to take any medications for twenty-four hours before the tests. Leukocyte histamine release was performed with ragweed antigen E by May and co-workers¹⁰ modification of the technique described by Lichtenstein and Osler,¹¹ as has been reported in detail previously. Dose-response curves were constructed from which the concentration of antigen E producing 50% histamine was interpolated. Leukocyte histamine release was repeated preseasonally and during the ragweed season.

* Courtesy of Drs. D. Marsh, L. Goodfriend, and T. P. King.

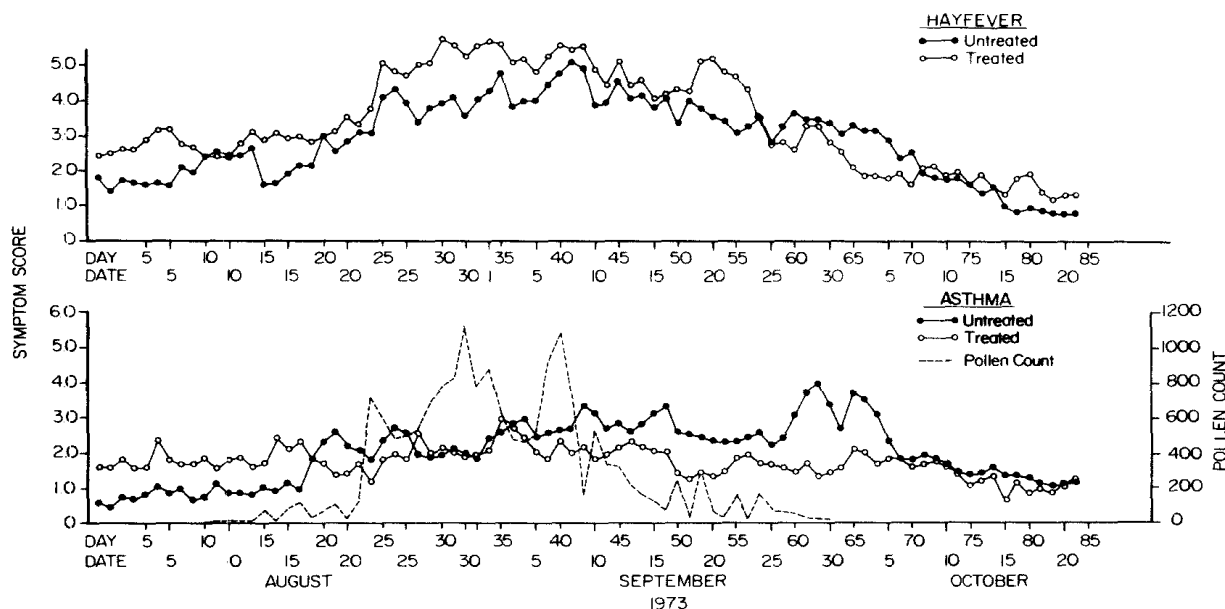


FIG. 3. Asthma and hay fever symptoms for treated patients (*open circles*) and untreated patients (*closed circles*) compared to ragweed pollen count (*dashed line*) for 1973 (July 30 to October 15).

Specific antiragweed IgE was kindly measured by Dr. Kimishige Ishizaka on serum taken at each bleeding. Methods used have been previously described.¹² Serum IgG blocking antibody was measured by radioimmunoassay, as previously described.¹³ Briefly, this involves the reaction of ¹²⁵I-labeled antigen E with dilutions of the serum to be assayed. The labeled antigen which is bound to IgG is precipitated with a gamma chain specific anti-serum in the presence of carrier IgG. The titer is the interpolated value for the reciprocal of the serum dilution which binds 50% of the antigen.

Inhalation bronchial challenge tests were performed using a variable pressure body plethysmograph to determine specific airways conductance (S_{GAW}), as previously described.^{14, 15} Patients inhaled dilutions of crude ragweed pollen extract (Center lyophilized lot No. 16608 FD). The cumulative provocation dose of antigen producing a 35% decrease in S_{GAW} was designated the PD_{35} . Antigen dose is expressed in g_{AW} , with one unit defined as one breath of a one microgram protein nitrogen per milliliter ragweed extract solution. Provocation tests were repeated prior to the 1973 ragweed pollen season.

The patients were paired on PD_{35} values and randomly assigned to either a treatment or a placebo group. New patient pairs were added to the study through March, 1973. Patients received weekly injections from January through August of 1973 of either aqueous ragweed extract (derived from Center lyophilized lot No. 16608 FD, and containing 10 μg AgE/ml or 3570 PNU/ml) or color-matched placebo containing histamine.

Symptoms and signs were evaluated on biweekly physician examinations during the 1973 ragweed pollen season. Patients were questioned about hay fever and asthma symptoms and medications taken. Physical examination of the eyes, nose, and lungs was performed, and the peak flow measured on a Wright peak flow meter. Points were

assigned to all findings as follows: one-half point for very slight, one point for slight, two points for moderate, and three points for severe symptoms. One to three asthma attacks equal one point; four to six attacks equal two points; seven or more attacks equal three points. Each 4 mg chlorpheniramine or 200 mg aminophylline equivalent taken daily equaled one point. Other medications (decongestants, steroids, ephedrine, nebulized bronchodilators) were scored similarly. Peak flow data were compared to preseasonal observations. The average of three attempts was determined. No points were assigned for a 0% to 10% decrease in the average peak flow. One point was assigned for a 10% to 25% decrease in peak flow; two points for a 26% to 40% decrease; and three points for a 41% or greater decrease in peak flow. Individual and composite scores were obtained for the hay fever and asthma.

For ten weeks between the first of August and mid-October of 1973, the patients recorded symptoms twice daily on diaries.⁹ Patients reported duration of difficulty breathing and cough, number and duration of asthma attacks, amount of sputum produced, duration of sneezing, stuffy or runny nose, red itchy eyes, and medication taken for asthma or hay fever. Diaries were returned weekly, scored, and data analyzed by computer to obtain scores for hay fever and asthma separately. An average of daily scores was obtained for each individual for hay fever and asthma to provide numbers which would characterize his hay fever and asthma. In each of the treatment groups daily scores were averaged to provide a series of daily averages which would characterize hay fever and asthma for the group.

Daily pollen and spore counts were performed from slides located on a suburban Baltimore Rotoslide sampler. For the 1973 data, a correlation coefficient (r) was determined for daily pollen count and both hay fever and asthma symptoms. Twenty-six patients (12 treated, 14

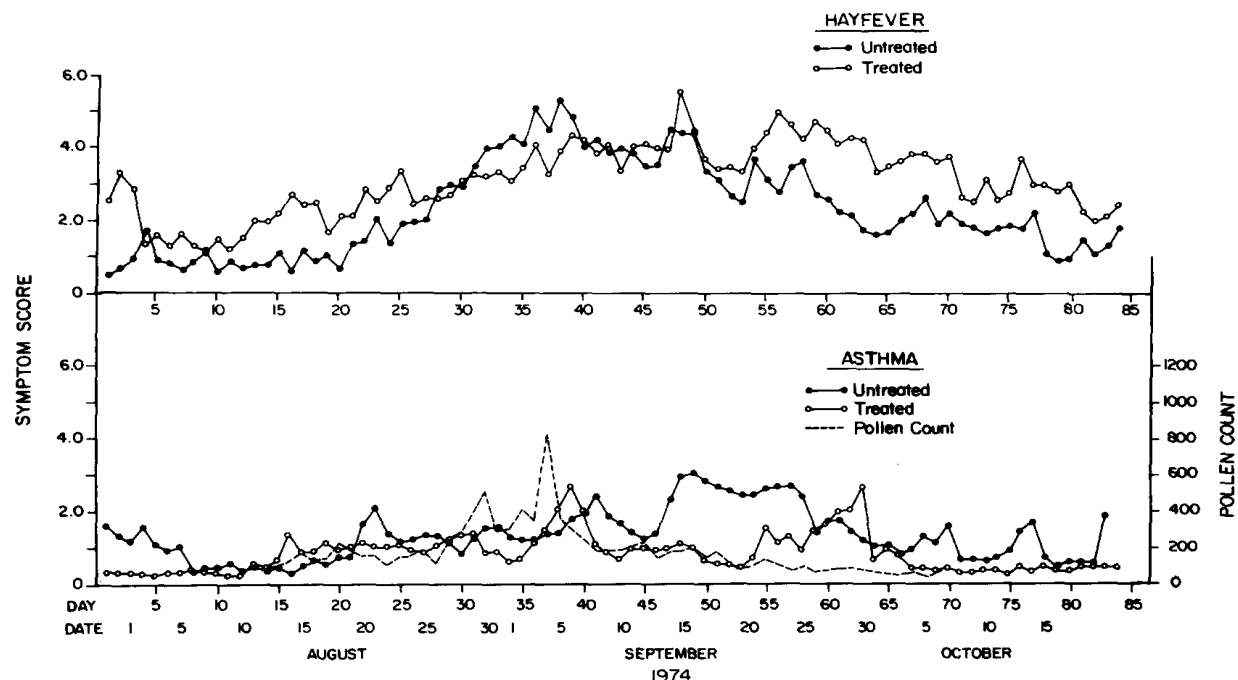


FIG. 4. Asthma and hay fever symptoms for treated patients (*open circles*) and untreated patients (*closed circles*) compared to ragweed pollen count (*dashed line*) for 1974.

placebo) continued weekly injections through the 1974 ragweed season. Ten placebo patients and 11 treated patients had bronchial challenge tests repeated prior to the 1974 ragweed season. Eighteen patients (10 placebo and 8 treated) kept daily symptom diaries during the 1974 ragweed pollen season.

RESULTS

During the course of injections of ragweed extract rises in dose were limited by local or systemic reactions more often than we have usually encountered in hay fever studies. In retrospect these reactions were not more severe than seen in hay fever patients but more persistent at a given dose. The reasons for this are not clear because groups of hay fever patients equally sensitive to ragweed extract by skin test or histamine release have participated in earlier studies and received larger doses without serious reaction.⁹ Furthermore, a comparison of these asthmatic patients with a group of hay fever patients with similar levels of total IgE antibodies did not demonstrate that the asthmatic patients were more commonly sensitive to minor allergens of ragweed.²² The mean cumulative dose in terms of antigen E was 11.7 μg (4,180 PNU) in 1973 and 31.2 μg (11,140 PNU) in 1974 (Fig. 1). From our earlier estimate that ragweed extract equivalent to 50 μg antigen E is required for the best results in hay fever,¹⁶ our doses were lower than optimum but nevertheless higher than the dose of 2,442 PNU that produced a statistically significant result in one of our earlier studies.⁹

Fig. 2 shows the 1973 individual and mean hay fever and asthma physician evaluation scores for the treated and placebo patients. Though the placebo patients' mean hay fever score was less (8.9) than the treated patients (11.6), the difference was not significant. In addition, the mean asthma scores for the two groups was not significantly different—4.4 for the treated patients versus 4.1 for the placebo patients. Analysis of the symptom diary data for the 1974 ragweed season, although for a small number of patients, again showed no significant difference in hay fever or asthma symptoms in the two groups of patients.

Fig. 3 shows a comparison of the daily average of hay fever and asthma scores. Comparison of these group averages with the pollen counts shows that asthma scores and pollen exposure have essentially no relationship. In fact, the placebo group had the highest asthma scores about the time pollen count declined to zero. Hay fever scores did peak at the time pollen counts were highest but were not very high for the level of sensitivity demonstrated by these patients. Fig. 4 shows a similar plot for 1974 and demonstrates a more evident lack of relationship between pollen count and symptom scores. Inspection of data from individual patients showed great variability in the day or days of appearance of peak severity of symptoms; hence in each patient, correlation coefficients between semiquantitative counts of aeroallergens and symptoms were calculated.

Fig. 5 is a composite graph showing daily counts of ragweed pollen and four mold spores identifiable

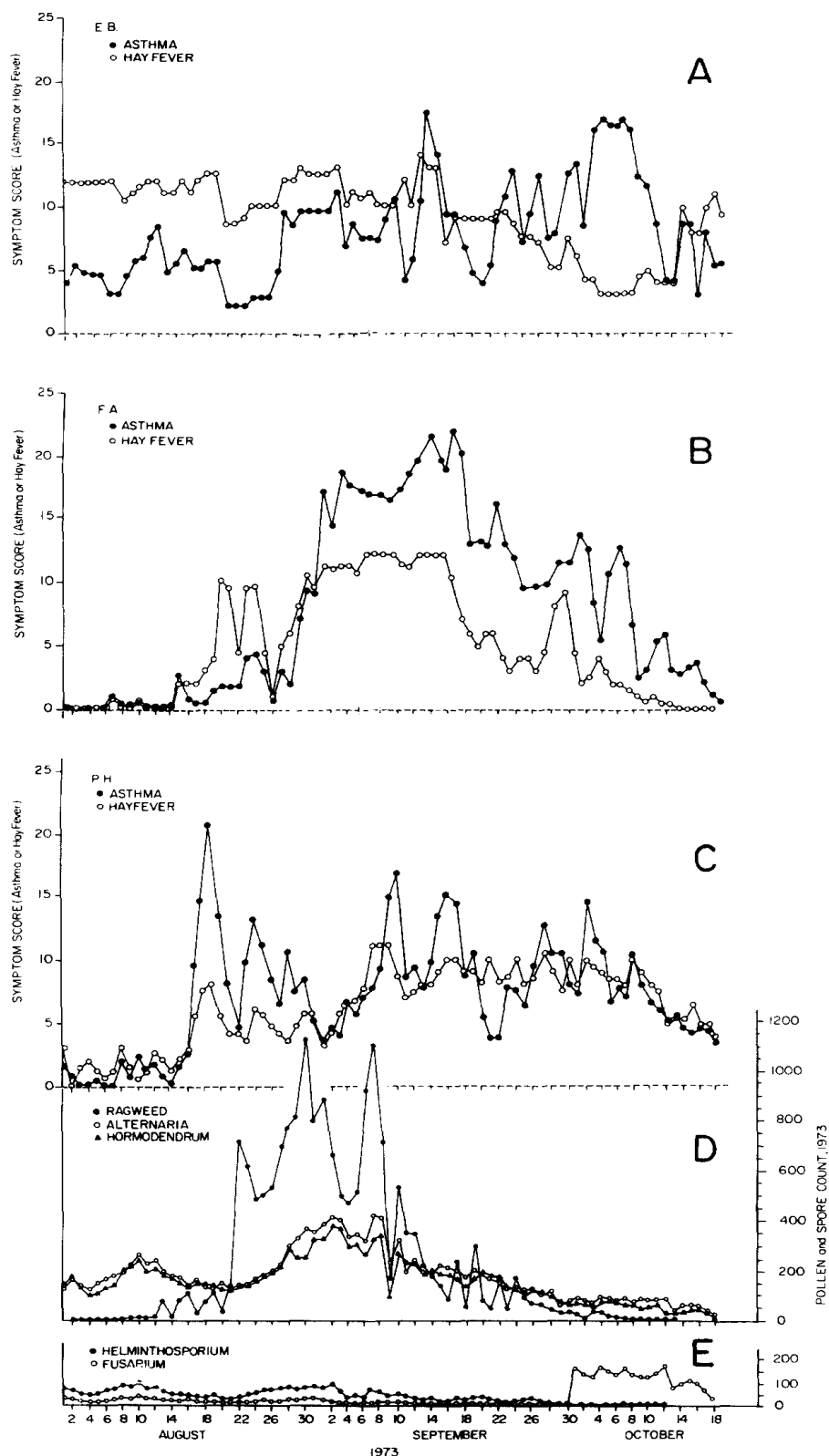


FIG. 5. *A*, Asthma symptoms (closed circles) and hay fever symptoms (open circles), Patient E. B., August to October, 1973. *B*, Asthma symptoms and hay fever symptoms, Patient F. A., August to October, 1973. *C*, Asthma symptoms and hay fever symptoms, Patient P. H., August to October, 1973. *D*, Ragweed pollen count (closed circles), *Alternaria* spore count (open circles), and *Hormodendrum* spore count (closed triangles) for August to October, 1973. *E*, *Helminthosporium* spore counts (closed circles) and *Fusarium* spore counts (open circles) for August to October, 1973.

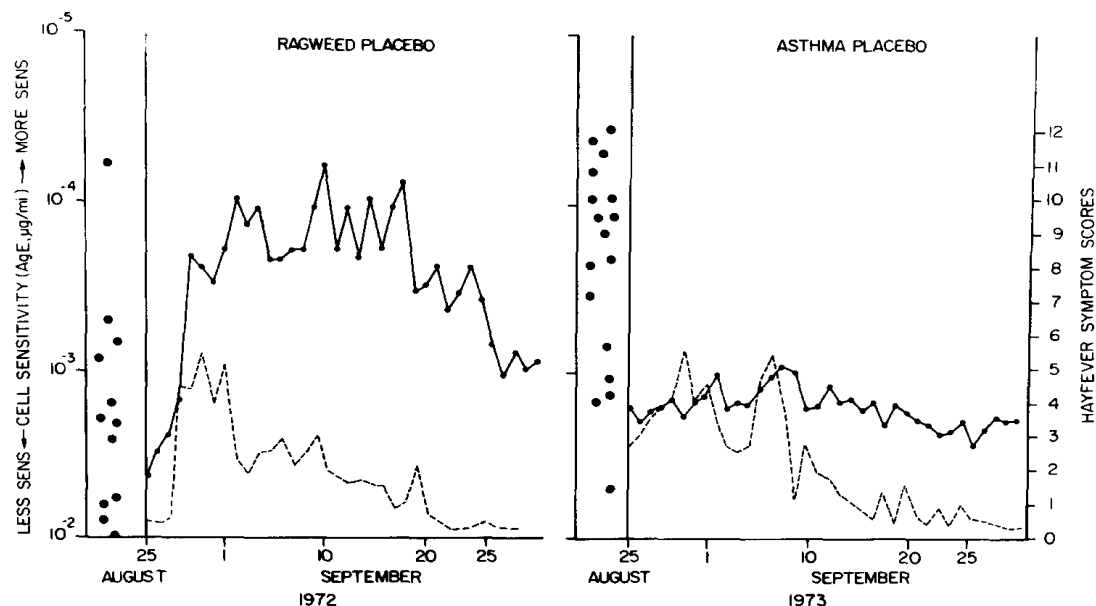


FIG. 6. Hay fever symptoms in group of 12 placebo-treated nonasthmatic allergic rhinitis patients, 1972, and 17 placebo-treated ragweed-sensitive asthmatic patients, 1973. Ragweed pollen count indicated for both years by dashed line. Cell sensitivity to ragweed antigen E indicated for each group of patients to left of symptom chart.

TABLE I. Correlation of symptoms with pollen or spore counts (1973)

Asthma	
Significant correlation with:	
Ragweed	13/29
<i>Alternaria</i>	15/29
<i>Hormodendrum</i>	15/29
<i>Fusarium</i>	6/29
Helminthosporium	9/29
Patients with no significant correlation	9/29
Hay fever	
Significant correlation with:	
Ragweed	19/29
<i>Alternaria</i>	20/29
<i>Hormodendrum</i>	20/29
<i>Fusarium</i>	2/29
Helminthosporium	15/29
Patients with no significant correlation	7/29

by morphology on the same time scale as hay fever and asthma scores in 3 patients to illustrate the variability in patients reporting the symptom. Fig. 5, A is Patient E. B., whose asthma symptoms correlated significantly only with *Fusarium* ($r = 0.417$, $p < 0.01$), while the hay fever symptoms correlate significantly with ragweed ($r = 0.373$, $p < 0.01$) and *Alternaria* ($r = 0.599$, $p < 0.01$). Fig. 5 B is Patient F. A., whose asthma and hay fever symptoms both correlated significantly with ragweed ($r = 0.382$,

$p < 0.01$ for asthma, $r = 0.660$, $p < 0.01$ for hay fever), *Alternaria* ($r = 0.462$, $p < 0.01$ for asthma, $r = 0.65$, $p < 0.01$ for hay fever), and *Hormodendrum* ($r = 0.467$, $p < 0.01$ for asthma, $r = 0.648$, $p < 0.01$ for hay fever). Fig. 5, C is a third example, Patient P. H., whose asthma and hay fever symptoms correlated with none of the allergens counted during the reporting period. Fig. 5, D and E show the pollen and spore counts for comparison.

Table I shows the number of patients whose asthma and hay fever symptoms correlated significantly ($p < 0.01$) with each of the allergens sampled during the 1973 reporting period. Thirteen patients had asthma correlating significantly with ragweed, 15 with *Alternaria* and *Hormodendrum*, 6 with *Fusarium*, and 9 with helminthosporium. Nine patients had asthma correlating with none of the allergens. Nineteen patients had hay fever correlating with ragweed, 20 with *Alternaria* and *Hormodendrum*, 2 with *Fusarium*, and 15 with helminthosporium. Seven had hay fever that correlated with none of the allergens.

Asthma and hay fever symptoms significantly correlated with each other in 24 of the 29 patients.

Fig. 6 shows a comparison of hay fever symptoms in a group of 12 ragweed hay fever, nonasthmatic, untreated patients from a 1972 study of ragweed hay fever and 17 untreated ragweed-sensitive asthmatic patients from the 1973 ragweed asthma study. To the left of each symptom chart is shown the cell sensitivity of the patients as determined by antigen E-induced histamine release. Although there are

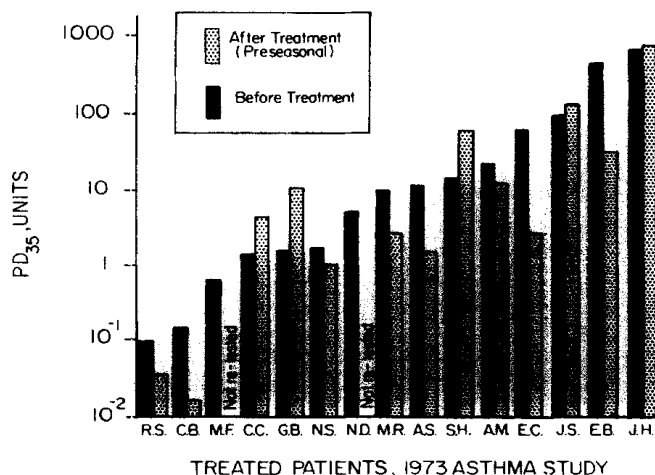


FIG. 7A. Provocation dose of ragweed extract causing 35% decrease in airways conductance in 15 treated patients: solid bar, baseline; dotted bar, posttreatment.

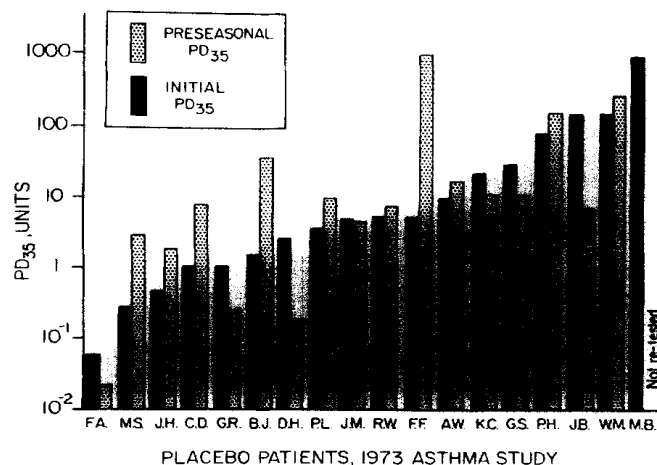


FIG. 7B. PD₃₅ in 18 untreated patients.

more highly sensitive patients in the ragweed asthma group, the hay fever symptoms are much less in the asthmatic group in 1973 than in the nonasthmatic group in 1972. Ragweed pollen counts are depicted by dashed lines in both groups and are similar for both years.

No significant correlation of asthma symptoms and ragweed allergen-related PD₃₅ values, skin tests, leukocyte histamine release, or RAST values was demonstrable in the treated or untreated patients.

Fig. 7A shows the PD₃₅ values before treatment (solid bar) and preseasonal, posttreatment (dotted bar) for the 15 patients in the 1973 ragweed treatment group. Two patients refused to have repeat bronchial challenge tests performed. Since there is a tenfold day-to-day variation in PD₃₅ values,¹⁴ to be significant a change must be greater than tenfold. No treated patients showed a significant improvement in ragweed-induced PD₃₅ values. Two patients (E. C. and E. B.) were significantly more sensitive on rechallenge.

Fig. 7B shows initial and preseasonal PD₃₅ values for 18 placebo patients. One patient declined repeat bronchial challenge. Three patients (M. S., B. J., and F. F.) showed significantly increased bronchial tolerance for ragweed allergen inhalation, despite no treatment, while 2 patients (D. H. and J. B.) were significantly more sensitive on repeat bronchial challenge.

Fig. 8 is a summary of the change in PD₃₅ values in the treated and untreated patients from the initial PD₃₅ to the 1973 preseasonal PD₃₅ values. Increased values indicate patients able to tolerate more ragweed on repeat challenge, therefore being less sensitive. Decreased PD₃₅ indicates patients requiring less rag-

weed allergen on repeat challenge, therefore being more sensitive.

Fig. 9 depicts the baseline and 1973 preseasonal concentration of ragweed antigen E required for 50% basophil leukocyte histamine release (cell sensitivity) for the treated and placebo groups of patients. No patients in the treated group showed tenfold or greater change in cell sensitivity. Six patients in the placebo group showed significant decrease in cell sensitivity, though 2 of these 6 were low histamine releasers (less than 50% maximum). One patient was significantly more sensitive on repeat measurement.

Fig. 10A shows the baseline and 1973 midseasonal (September) concentration of IgE antibody against ragweed in the two groups of patients. Only 1 of the 15 treated patients demonstrated a significant drop in specific IgE antibody after treatment with ragweed extract, while one other patient showed a slight decrease in IgE titer. No significant decrease in specific IgE antibody levels occurred in the 16 placebo patients. Data from 2 other patients in the placebo group were incomplete. The remainder of the patients in both groups manifested the usual rise in specific IgE after seasonal exposure to ragweed pollen.

Fig. 10B shows baseline and midseasonal IgG blocking antibody titers for the treated and placebo patients shown in Fig. 10A. Eleven of 15 treated patients made blocking antibody, although levels produced were less than in prior studies,¹⁶ probably reflecting the lower doses of antigen E received by these patients. Contrary to our usual experience with untreated patients,¹⁶ 6 of 16 placebo patients had detectable blocking antibody titers. These values could represent response to antigen delivered via bronchial challenge.

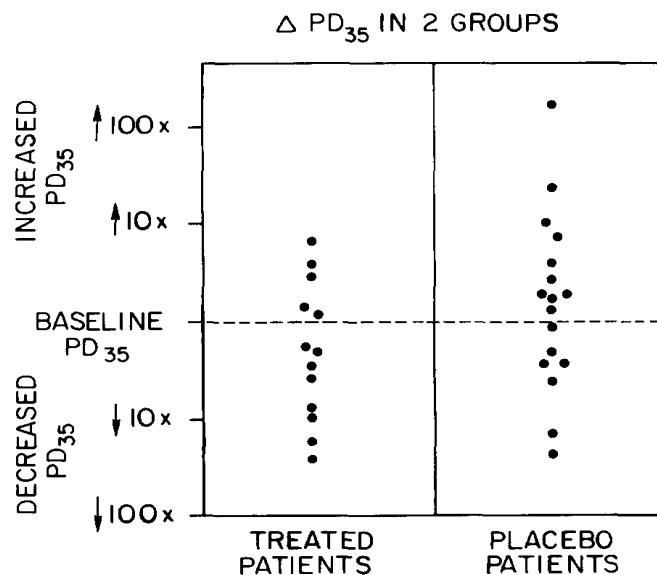


FIG. 8. Change in preseasonal, posttreatment, or post-placebo PD_{35} from baseline in treated and untreated patients.

Of 26 patients continuing the study through the 1974 ragweed season, 21 patients had repeat bronchial challenge tests done. Three of 10 placebo patients demonstrated significant decrease in bronchial sensitivity as measured by PD_{35} , while 2 of 11 treated patients showed significant decrease in bronchial sensitivity. One treated patient was significantly more sensitive on repeat bronchial challenge.

DISCUSSION

We have used symptom diaries for the evaluation of results of immunotherapy for hay fever for a number of years, obtaining good correlations with immunologic data.⁸ Therefore, the same basic method was applied to the study of asthma symptoms in our study patients. Symptomatic evaluation of patients by physicians and by daily symptom diaries correlated significantly ($p < 0.01$) with each other. Both methods failed to show significant difference in the treated and placebo groups in regard to hay fever or asthma symptoms. Although this failure to improve the treated patients may reflect the modest dosage of allergen administered, it probably is also due to the involvement of allergens other than ragweed in the production of symptoms. Fig. 5 shows a plot of the ragweed and spore counts in Baltimore from July 30 through October 20, 1973. When each patient's asthma and hay fever scores were examined individually, the pattern of symptoms was found to be quite variable from patient to patient, and quite unlike the more or less uniform pattern we have noted previously in patients with relatively pure hay fever and

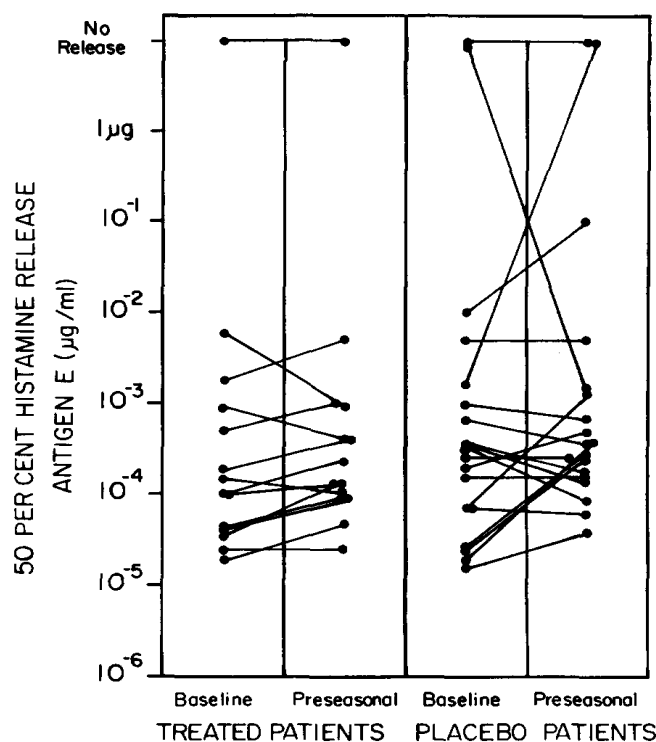


FIG. 9. Pre- and posttreatment cell sensitivities (concentration of antigen E required for 50% leukocyte histamine release) in treated and placebo patients (1973 season).

ragweed sensitivity.⁸ Despite the fact that all patients were sensitive to ragweed by skin test, leukocyte histamine release, and inhalation bronchial challenge, only 13 of the patients had asthma symptoms which correlated significantly with ragweed counts. Robertson and co-workers¹⁷ reported late asthmatic responses in 9 of 15 ragweed-allergic asthmatic patients after inhalation challenge with ragweed. Taking this into consideration, we looked at the 13 patients in our study who reported delayed asthma after bronchial challenge to see if they were the ones whose symptoms failed to correlate with pollen counts. This was not the case, however.

Patterns of symptoms are shown for 3 individual patients in Fig. 5. The variability in symptom patterns is impressive though all are ragweed-allergic by objective methods. All three have seasonal asthma in the late summer or early fall, but only 1 of the 3 (F. A.) has asthma symptoms correlating with the ragweed pollen count, and this patient consistently reported delayed asthma for several days after inhalation challenge with very small doses of ragweed extract. A summary of the correlations of asthma and hay fever symptoms is shown in Table I for the entire group. Those 9 patients reporting asthma correlating with none of the allergens counted may have

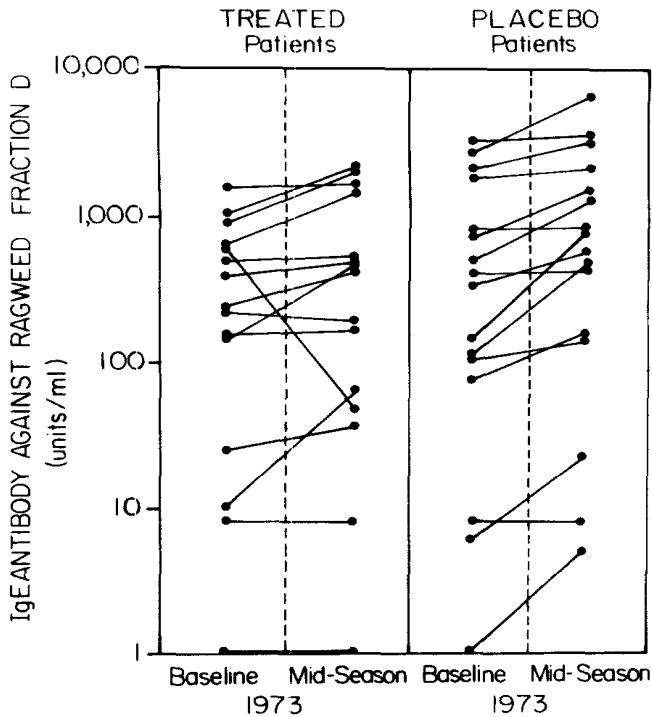


FIG. 10A. Baseline and midseason 1973 (September) IgE antibody against ragweed fraction D in RAST U/ml for treated and untreated patients.

symptoms from allergens not identified by our air sampling techniques, such as spores of *Basidiomycetes*, as reported by Lopez, Salvaggio, and Butcher,¹⁸ or from other causes.

The failure of asthma symptoms to correlate with ragweed pollen counts does not mean that ragweed antigens are not involved in the production of asthma symptoms in some of these patients, although whole pollen grains are too large to penetrate airways significantly.¹⁹ In the laboratory ragweed-sensitive asthmatic patients have failed to respond to inhalation of whole pollen grains with asthma symptoms but have done so after inhaling fragmented pollen.²⁰ It has been reported²¹ that fragments of ragweed pollen or plant particles may be present in the air and may be the cause of allergic symptoms. If particulates of this kind were important in seasonal asthma, one might expect most of the patients to have their asthma during the same period, even though that period might be different from the maximum pollen count. Actually in our patients, the period of maximum symptoms came any time during the course of the reporting period covered by the study. This finding may be interpreted as responses to one or more different allergens in each patient, or to the nonallergic factors often mentioned in discussions of the pathogenesis of asthma.

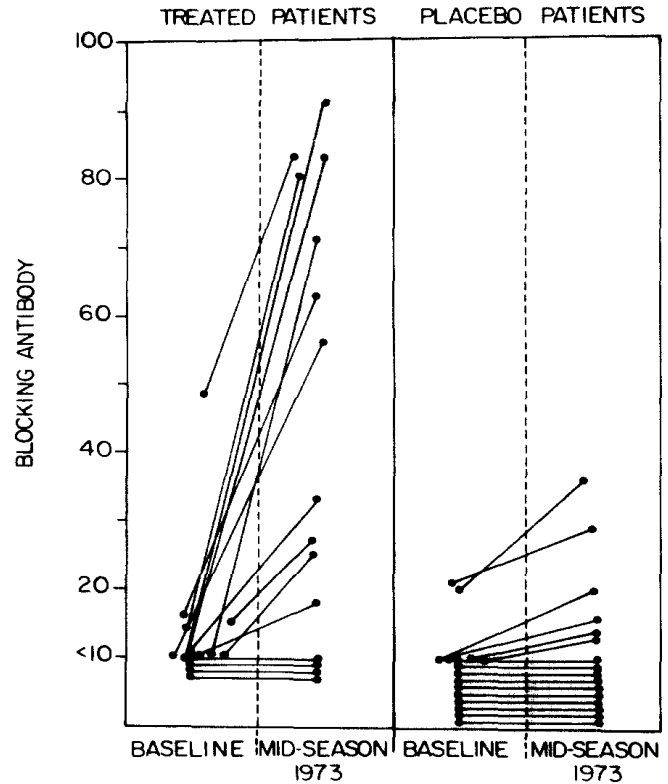


FIG. 10B. Baseline and midseason 1973 serum IgG blocking antibody titers against ragweed as determined by radioimmunoassay in treated and placebo patients. Blocking antibody expressed as reciprocal of the serum dilution required for 50% finding of antigen E.

A puzzling finding is that symptoms of hay fever in these patients who also have asthma, when compared to symptoms of ragweed-allergic patients with no asthma, are significantly lower than expected (Fig. 6). Indeed, the hay fever symptom pattern in this group, who also are asthmatic, is more like that of a group of poor histamine releasers studied in 1970. These findings point to the complexity of the patients who have rhinitis and asthma, as compared to those with only rhinitis.

Hay fever and asthmatic patients, however, did *not* differ in sensitivity to three of the allergens found in ragweed pollen. The asthmatic patients reported here were subjects for a comparison with an equal number of hay fever patients matched on the basis of similar total serum IgE levels. Leukocyte sensitivity to antigen E, and skin test sensitivity to antigens E, Ra3, and Ra5, were not significantly different in the two groups.²²

Our data in regard to change in bronchial tolerance after treatment is in contrast to the reports of Citron, Franklin, and Sinclair⁵ and Aas.⁷ When only tenfold or greater changes in bronchial tolerance are considered significant, our data are similar to those of

McAllen⁶ in regard to grass pollen asthmatics. None of our patients who were treated preseasonally in 1973 with ragweed extract showed significant increase in bronchial tolerance as determined by PD₃₅. A possible explanation for this failure to change PD₃₅ values significantly is that patients did not receive adequate dosage of allergen. The maximal pre-seasonal dose of 39 μ g of antigen E was achieved by only 3 patients in the treatment group. The mean dose for the entire treatment group was much less, only 11.72 μ g. This dosage is only about 20% of the 50 μ g of antigen E usually we have considered optimum to ameliorate significantly symptoms in ragweed hay fever patients.¹⁶ The failure to prevent some seasonal rises in specific IgE antibody titers against ragweed (Fig. 10A) provides further evidence that the dosage of immunotherapy was inadequate in many patients.

We did find 6 patients who significantly changed their cell sensitivity to ragweed antigen E as measured by leukocyte histamine release; all of these patients were untreated. This finding is in contrast to our prior experience with ragweed hay fever patients.¹⁶ Two of the 6 patients were low histamine releasers (less than 50%) as were 2 of the placebo patients whose PD₃₅ significantly increased.

Another contrast with hay fever is that no significant correlation exists between any objective measurements of sensitivity—ragweed allergen related PD₃₅ values, skin tests, leukocyte histamine release, or RAST—and asthma symptoms, despite the fact that these measurements correlate quantitatively with each other.¹⁵ This again points to the complex nature of apparently simple seasonal asthma. Since none of the objective measurements of allergy to ragweed appear to be predictive of disease severity in these patients, the establishment of specific allergic etiology of symptoms can be confirmed only by careful following of symptom patterns throughout the pollen season. In such a setting, results of immunotherapy with a single agent in patients with fall asthma is almost impossible to study. Furthermore, we doubt that the Baltimore area contains large numbers of patients with simple ragweed asthma. We called for volunteers for this study because such patients have been uncommon in our clinic. Our patients were first selected from over three hundred adult volunteers to a call for patients with autumnal asthma. Only 79 of this group gave a satisfactory seasonal history when interviewed. The group was further reduced when only 41 patients showed good skin tests and immunologic evidence of ragweed sensitivity. We obtained the participation of 39 of these patients through the first season. It is, of course, possible that ragweed

plays a greater role in asthma in children or in areas where pollen exposure is higher. We think it is more likely that most autumnal asthma is a multifactorial disease and is, therefore, unlikely to respond to immunization with a single allergen.

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